VASCULAR SMOOTH MUSCLE RELAXATION IN SOLUBLE GUANYLYL CYCLASE ALPHA 1 KNOCKOUT MICE

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Soluble guanylyl cyclase (sGC), the predominant receptor for nitric oxide (NO), consists of an α and a β subunit, each existing in 2 isoforms (α1/α2 and β1/β2). In order to investigate the functional importance of the _1-subunit in vasorelaxation, aortic segments from male and/or female sGCα1$^{-/-}$ mice and wild type littermates were mounted for isometric tension recording in a small vessel myograph. The relaxing influence of both exogenous NO (from sodium nitroprusside (SNP) and NO-gas) and endogenous NO (released from the endothelium in response to acetylcholine (ACh)), were significantly decreased in the sGCα1 knockout mice of both genders. However, hypertension only developed in the male sGCα1$^{-/-}$ mice. In the presence of the sGC-inhibitor ODQ, the difference in ACh- ,SNP- and NO-gas induced response between the sGCα1$^{-/-}$ and wild type mice was significantly reduced. The responses to the NO-independent sGC-activator (BAY 41–2272 and YC-1) were also significantly reduced in the aorta from sGCα1$^{-/-}$ mice. Relaxations in response to the KATP-channel opener levcromakalim and the cGMP-analogue 8-pCPT-cGMP were similar, indicating the specificity of the impairment of the sGC-related responses. Measurements of cGMP concentrations showed significantly lower basal and SNP stimulated levels in the sGCα1$^{-/-}$ mice. ODQ was able to reduce the amount of cGMP evoked by SNP. The results indicate the involvement of an sGC isoform with the α1-subunit in NO-induced vasorelaxations. However, the substantial relaxation remaining in sGCα1$^{-/-}$ mice suggests the contribution of (an) additional pathway(s).